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Late-Onset Alcohol Abuse as a Presenting Symptom of Neurodegenerative Diseases

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Abstract

Background: The association between lifetime alcohol abuse and a higher risk to develop dementia is well known. However, it is unknown whether older adults who begin abusing alcohol late in life have an underlying neurodegenerative disease.

Objective: Identify the frequency of lifelong alcohol abuse (L-AA), late-onset alcohol abuse (LO-AA), and alcohol abuse as a first symptom of dementia (AA-FS) in patients with neurodegenerative diseases.

Methods: Cross-sectional retrospective study of patients evaluated at an academic referral center with a clinical diagnosis of behavioral variant frontotemporal dementia (bvFTD), Alzheimer-type dementia (AD), and semantic variant primary progressive aphasia (svPPA) (n = 1,518). The presence of alcohol abuse was screened with the National Alzheimer's Coordinating Center questionnaire. L-AA was defined as onset < 40 years, LO-AA as onset ≥40 years, and AA-FS was defined when the abuse started within the first three years from symptom onset.

Results: The frequency of LO-AA was 2.2% (n = 33/1,518). LO-AA was significantly more frequent in patients with bvFTD than AD (7.5%, n = 13/173 versus 1.3%, n = 16/1,254, CI:1.0;11.4%), but not svPPA (4.4%, n = 4/91, CI: −4.4;10.7%). Similarly, AA-FS was more

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SUPPLEMENTARY MATERIAL

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frequent in bvFTD patients than AD (5.7%, *n* = 10/173 versus 0.7%, *n* = 9/1,254, CI:0.5%;9.5%), but not svPPA (2.2%, *n* = 2/91, CI:–2.4;9.1%).

Conclusion: LO-AA can be a presenting symptom of dementia, especially bvFTD. Alcohol abuse onset later in life should prompt a clinical investigation into the possibility of an underlying neurodegenerative process because delay in diagnosis and treatment may increase patient and caregiver burden. The results need to be interpreted with caution due to the limitations of the study.

Keywords

Alcohol-related problems; Alzheimer's dementia; dementia; frontotemporal dementia

INTRODUCTION

Among the symptoms that occur in patients with behavioral variant frontotemporal dementia (bvFTD), compulsive behavior and hyperorality are common [1, 2] and may manifest as an increase in, or a new onset of, alcohol consumption [3]. Patients with semantic variant primary progressive aphasia (svPPA), a disorder characterized by progressive loss of semantic knowledge [4], may also increase their alcohol consumption [5]. Yet, in the absence of obvious behavioral changes or cognitive decline, a neurodegenerative disease is rarely suspected when older adults start abusing alcohol for the first time, or unexpectedly increase their alcohol consumption. Conversely, patients with Alzheimer's disease dementia (AD) usually have preserved social and emotional processing until late in the disease [6]. However, patients with AD can also present with mood disorders [7], which is often associated with alcohol abuse [8]. Therefore, it is not clear whether alcohol abuse would be less frequent in patients with AD compared with patients with bvFTD and svPPA.

Overall alcohol abuse is present in 1.7% of older adults in the United Stated [9] and the prevalence of hazardous drinking can be as high as 21.5% in older adults in Europe [10]. Lifelong alcohol abuse (L-AA) is a risk factor for dementia [11, 12]; however, the frequency of late-onset alcohol abuse (LO-AA) as a possible presenting symptom of bvFTD, svPPA, and AD has not been systematically explored. People who begin abusing alcohol because of an underlying neurological condition may be misdiagnosed with primary alcohol abuse and referred to traditional addiction treatment programs, a process that may delay correct diagnosis and appropriate behavioral treatment, expend family resources, and add to patient and caregiver burden. This study aimed to identify and compare the frequencies of L-AA, LO-AA, and alcohol abuse as a first symptom of dementia (AA-FS) in a cohort of patients with bvFTD, svPPA, and AD.

METHODS

Study participants

Participants were evaluated at the Memory and Aging Center, at the University of California, San Francisco (UCSF) between 1999 and 2017. First, we identified all participants who had completed the National Alzheimer's Coordinating Center Uniform Dataset (UDS) questionnaire and had participated in one of two NIH/National Institute of Aging-funded

studies: the program project grant “Frontotemporal Dementia: Genes, Images and Emotions” (PPG, P01-AG1972403; PI: Miller) and the UCSF Alzheimer’s Disease Research Center grant (ADRC, P50-AG023501; PI: Miller). Then we selected the participants who had a clinical diagnosis of AD, bvFTD, or svPPA based on accepted diagnostic criteria [1, 4, 13] and as determined by a multidisciplinary consensus panel after a detailed neurological and neuropsychological examination. Four participants did not have charts available and were excluded. Our final sample had 1,518 participants of whom 1,254 had a clinical diagnosis of AD, 91 had a diagnosis of svPPA, and 173 had a bvFTD diagnosis (Supplementary Figure 1). All participants or their assigned surrogate decision-makers signed an informed consent. The study was approved by the UCSF Institutional Review Board for human research and was performed according to UCSF Human Research policy.

Alcohol abuse assessment

The presence of alcohol abuse was screened using the National Alzheimer’s Coordinating Center UDS questionnaire that is completed by clinicians during patient research visits. Alcohol use is classified as abuse when alcohol consumption negatively impacts work or social life or leads to legal ramifications, based on patient/informant report, medical records, and observation. We reviewed the medical charts of participants who screened positive for alcohol abuse (AA) on the UDS. The chart review had the purpose of 1) confirming AA, 2) determining the age of onset of AA, 3) determining the age of dementia symptoms onset, and 4) assessing whether AA was a presenting symptom of dementia. We did not review the charts of participants who screened negative for alcohol abuse.

Participants were classified into three groups: 1) no AA, 2) L-AA, defined as onset of AA before the age of 40, and 3) LO-AA, defined as onset of AA at the age of 40 or later. The cutoff of 40 was chosen because a prospective study showed that 90% of people who abuse alcohol do so by the age of 30 [14] and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V) states that most persons with AA disorders develop this condition before the age of 30 [15]. We allowed an additional 10 years in order to remain conservative since the majority of patients with early-onset dementia will have their first symptom after the age of 40 [16-18]. Although AA is not considered a classic symptom of dementia, we classified a subgroup of participants in whom alcohol abuse was a presenting symptom of dementia, when the alcohol abuse started within 3 years of the onset of cognitive or behavioral changes. We chose the time window of 3 years to parallel the suggested timeframe of symptoms considered early in the bvFTD diagnostic criteria [1].

It was not possible to determine the exact age of onset of alcohol abuse for a total of 83 participants screened positive for alcohol abuse per the UDS questionnaire. Of those 83, in 66 participants (54 with AD, eight with bvFTD, and four with svPPA) it was clear in the chart that the alcohol abuse started in the patient’s youth, although the exact age of onset could not be determined. The remaining 17 (14 with AD, two with bvFTD, and one with svPPA), for whom there was no mention of age of onset in the chart, were also classified as L-AA in order to remain conservative and because clinicians will frequently not document the age of onset of AA for people with a lifelong history of alcoholism.

Genetics assessment

A subgroup of participants received genetic testing as part of their research protocol. For these patients, we collected available information regarding Apolipoprotein E and Tau haplotype status. We also collected information regarding the presence of a mutation in any of the AD autosomal dominant genes (*APP*, *PSEN1*, and *PSEN2*), and in any of the frontotemporal lobar degeneration (FTLD) autosomal dominant genes (*FUS, GRN, MAPT*, and *TARDBP*), as well as the presence of pathological hexanucleotide repeat expansion in *C9orf72* as previously described [19].

Neuropathological assessment

The neuropathological diagnosis was available for most deceased participants. The neuropathological assessment includes an extensive investigation of brain regions known to be affected by neuropathological changes that cause dementia. The neuropathological diagnosis was made per currently accepted guidelines [20-24]. Subtyping for FTLD-TDP and FTLD-tau followed the current “harmonized” nomenclature [25, 26].

Statistical analysis

The frequency of overall AA, L-AA, LO-AA, and AA-FS were calculated for the whole sample, and separately for patients with bvFTD, svPPA, and AD. We used the Mann-Whitney Test to compare differences in age of onset, education, and Mini-Mental State Examination (MMSE) at first visit. Chi-squared test was used to compare differences in gender. When the frequency of any variable was low, the Fisher’s exact test was used. Comparisons were made between the different dementia groups and the different alcohol status groups. The Bonferroni correction was used for multiple comparisons analyses. Associations between each dementia group and alcohol abuse status were examined using multivariable logistic regression with alcohol abuse status as the outcome, dementia diagnosis as the predictor variable, AD as the reference group, and age of dementia onset, MMSE at first visit, gender, and years of education as covariates. The svPPA group was not used as the reference because of the small group size.

Statistical analyses were carried out on the statistical package R Studio (Version 1.1.414–©2009–2018 RStudio, Inc) [27] and the level of significance was set at $p < 0.05$ two-sided.

Data availability

All the raw data that supported the findings can be made available for qualified researchers upon reasonable request.

RESULTS

Frequency of alcohol abuse

Among the 1,518 participants screened, the mean age of dementia symptoms onset was 66.8 (Standard deviation (SD)±11.4) and 45.1% (685/1,518) were male. The overall frequency of AA was 8.4% ($n = 128$), 6.2% among women and 11.1% among men. The overall frequency of LO-AA was 2.2% ($n = 33$) and was gender-balanced. Patients with LO-AA were significantly younger and more educated than those with no AA (Table 1). More

women had LO-AA than L-AA, but this difference was not significant. A higher proportion of people with bvFTD than AD had LO-AA (7.5%, n = 13/173 versus 1.3%, n = 16/1,254, CI:2.1–8.3%, p = 0.004) (Fig. 1). In the bvFTD group, patients with LO-AA were more educated than those with L-AA (Supplementary Table 1).

In the LO-AA group, two thirds had AA-FS, which corresponded to a total of 1.4% of all participants (n = 21/1,518). AA-FS was more frequent in bvFTD than AD (5.7%, n = 10/173 versus 0.7%, n = 9/1,254, CI:0.5–9.5%, p < 0.001) (Fig. 1).

The frequency of L-AA was similar across dementia groups (7.5%, n = 13/173 in bvFTD, 6.1%, n = 77/1,254 in AD and 5.5%, n = 5/91 in svPPA, p = n.s).

In a multinomial logistic regression analysis with correction for cofounding variables, late-onset alcohol abuse was 4.6 times more likely to occur in patients with bvFTD than with AD (CI:1.8–11.4, p = 0.001). In the subgroup analysis, alcohol abuse as a possible presenting symptom of dementia was 5.3 times more likely to occur in patients with bvFTD than AD (CI:1.7–16.2, p = 0.003).

Clinicopathological correlation

Of the 39 patients with AA who were deceased, 28 had undergone autopsy. The pathological diagnosis was concordant with the clinical diagnosis in 92.8% (n = 13/14) of patients with AD. Of those, six patients had pure AD, five had AD plus Lewy body disease, and two had AD plus vascular disease. The one patient that was clinically classified as AD but did not have an AD pathological diagnosis had transactive response DNA-binding protein with 43 kD (TDP-43) type C and had L-AA. Of patients with pathological AD, three had LO-AA, of whom two had FS-AA and were AD without any co-pathology.

Among patients with bvFTD, 20% (n = 2/10) had FTLD-tau pathology (all Pick's disease); one had LO-AA and the other had L-AA. Seventy percent (n = 7/10) had FTLD with TDP-43 pathology. Five had TDP-43 type B, of whom three had AA-FS and two had L-AA. One patient had TDP-43 type A with AA-FS and one had TDP-43 unclassifiable that had L-AA. The other patient with bvFTD had a pathological diagnosis of argyrophilic grain disease and had L-AA.

Among patients with svPPA, 50% (n = 2/4) had FTLD TDP-43 type C pathology and had L-AA. The other 50% (2/4) had FTLD-tau and had AA-FS. The two latter were clinically atypical as one was diagnosed by a panel of clinicians as svPPA with bvFTD and the other as svPPA with atypical AD.

In summary, regardless of the clinical diagnosis, of the 10 patients with LO-AA with neuropathological data available, seven had FTLD pathology (four TDP-43 and three tau), two had AD and one had AD plus vascular disease (Fig. 2).

Genetic profile

Eighty out of the 128 patients with AA had genetic testing (28 with LO-AA and 52 with L-AA). None of the participants had *APP, PSEN2, FUS*, or *TARDBP* mutations. In

patients with LO-AA, one had a *PSEN1* mutation, one had a *GRN* mutation, and one had a *MAPT* mutation. In patients with L-AA, one had a *C9orf72* expansion, and one had an *MAPT* mutation. There was no difference in the proportions of Tau haplotype H1/H1 and Apolipoprotein E haplotype containing the ε4 allele between patients with LO-AA and L-AA (Supplementary Table 2).

DISCUSSION

LO-AA was present in 2.2% of this cohort of patients with neurodegenerative diseases, a proportion higher than the 1.7% that has been reported in older adults in United States [9]. We found LO-AA significantly more prevalent in bvFTD than AD while there was no difference between the frequency of L-AA across the three dementia groups. AA-FS occurred in 1.4% of all patients, five times more frequently in patients with bvFTD than AD. A previous study that looked only at patients with pathologically defined FTLD found that 4.1% of them had alcohol abuse as a possible presenting symptom of dementia [28]. Here we present for the first time an assessment of alcohol abuse in a well characterized cohort of patients with AD, bvFTD, and svPPA, including some cases with pathological confirmation, which allowed us to compare the frequencies of LO-AA among the three clinical syndromes and to infer that LO-AA might be one possible presenting symptom of those conditions, especially bvFTD.

Alcohol abuse is considered a risk factor for dementia [29-31], and the onset of AA in the elderly have been thought to be related to changes in social environment such as retirement, losses (income, housing, loved ones), or loneliness [32], which pre-dispose to mood disorders and AA [33]. We add to this list that AA may be the first sign of an underlying neurological condition when it presents late in life and should prompt clinicians to investigate the possibility of a frontal lobe dysfunction. Health care workers should avoid systematically attributing AA only to social aspects related to aging such as loneliness. Atrophy in regions commonly affected by bvFTD such as frontotemporal, striatal, and insular areas have been associated with addiction [34, 35]. Furthermore, dysfunctional reward processing caused by right ventral striatum degeneration has been proposed as a possible mechanism for AA in patients with bvFTD [3]. Lack of impulse control due to degeneration of fronto-limbic-striatal circuits in bvFTD might also play a role in AA [36]. Not surprisingly, LO-AA was most frequent in our bvFTD cohort, in which those networks are commonly affected.

In terms of neuropathological diagnosis, we also found a higher proportion of LO-AA and AA-FS in FTLD-TDP (mostly type B) and FTLD-tau (Pick's disease) when compared with AD. Although the numbers are too small to drive definitive conclusions, we can speculate that LO-AA as a prominent clinical feature is maybe due to the lesions in specific brain regions affected by those pathologies, not necessarily from the molecular signature.

It is important to distinguish the phenomenology of substance misuse and dementia with alcohol abuse. Behavioral addictions are characterized by harmful actions caused by an inability to resist an urge or drive [37]. Primary alcohol misuse was described to have three phases: an early phase characterized by increased tolerance, loss of flexibility, and salience;

a middle phase characterized by increased need for alcohol; and a late phase, marked by symptoms of physiological withdrawal, including nausea, tremors, and hallucinations [38]. Behavioral addictions can be considered a compulsive behavior, that presents in a different phenomenology in patients with dementia. In bvFTD, the compulsive behavior is more ritualistic, usually with lack of insight about the harmful consequences and associated with disinhibition and impaired intersocial boundaries [39], aspects that can be confounded by the effects of alcohol misuse. In AD, social disinhibition and inappropriate non-verbal communication [39] are rare, whereas major depression is common, and alcohol misuse could be wrongly attributed to be reactive to depressive symptoms. Indeed, often times it may be difficult for informants to distinguish symptoms of alcohol abuse and dementia. For instance, informants may misinterpret changes in functioning as related to the patient's drinking instead of reflecting symptoms of the underlying dementia.

The present study calls attention to an important topic, the possibility of LO-AA as a sign of a neurodegenerative disease. Some limitations of this work include the retrospective design with chart analysis, which prevented further characterization of AA and assessment of symptoms of dependence such as withdrawal and tolerance. Therefore, the phenomenology distinction between alcohol abuse and alcohol abuse in dementia could not be further explored. We did not have access to information about quantities of alcohol consumed nor to the psychosocial context when the patient started abusing alcohol (i.e., divorce, grief, loss of work, lack of social support). Selection bias might have occurred because we did not review the charts of participants whose UDS reported no AA. We did not have precise information about the current diagnosis of depression at the time alcohol abuse started, which could be a major limitation because alcohol abuse may often be associated with depression. Indeed, the results need to be interpreted with cautious, as both neurodegenerative diseases and alcohol abuse are complex conditions. Because each disease group (AD, bvFTD, and SD with LO-AA) had relatively small number of patients, the risk of not accounting for possible other confounding factors prevent definite conclusions. Finally, the age cutoff chosen for differentiating LO-AA from L-AA is not an accepted cutoff. However, it is informed by the literature as detailed in the Methods section. Considering that alcohol abuse is underdiagnosed in older adults [40] and might not have been reported in the UDS questionnaire, some patients that had alcohol abuse but answer "no" to the UDS questionnaire could have had documented AA in their chart and escaped our detection.

Suspecting that patients with LO-AA may have an underlying neurodegenerative disease can significantly impact medical management and patient outcome. Some symptoms of dementia such as disinhibition and difficulties multitasking can be initially attributed to alcohol effects, delaying the diagnosis of dementia. Furthermore, isolation from the family and poor compliance with rehabilitation programs may result from apathy, impaired impulse control, dysfunction in reward processing and lack of empathy, rendering patient management more challenging. Indeed, it has been reported that older adults are more responsive to rehabilitation than younger adults [31], which may not be the case in patients with neurodegenerative diseases, such as bvFTD. For instance, a meta-analysis about treatment of alcohol abuse in older adults showed that the interventions were mostly based on counseling and feedback [41], which may not be useful in patients with dementia.

Tailored treatments and special rehabilitation programs for people with dementia will probably be more efficient in patients with LO-AA and dementia.

To conclude, this study indicates that LO-AA is much more frequent in bvFTD than AD, and it is likely that the biological mechanism underlying LO-AA and L-AA are different. Because patients that begin abusing alcohol late in life are usually first seen by psychiatrists, primary care doctors, and rehabilitation clinics, these professionals should be aware of the possibility of a neurodegenerative disease as an etiology and should specifically inquire about other frontal lobe symptoms. Further, they should avoid automatically attributing other neuropsychiatric symptoms to alcohol abuse alone. An early and appropriate diagnosis in those patients is paramount for providing the best management, improving patients' and families' quality of life, avoiding iatrogenic consequences and isolation, and channeling patients to clinically appropriate care facilities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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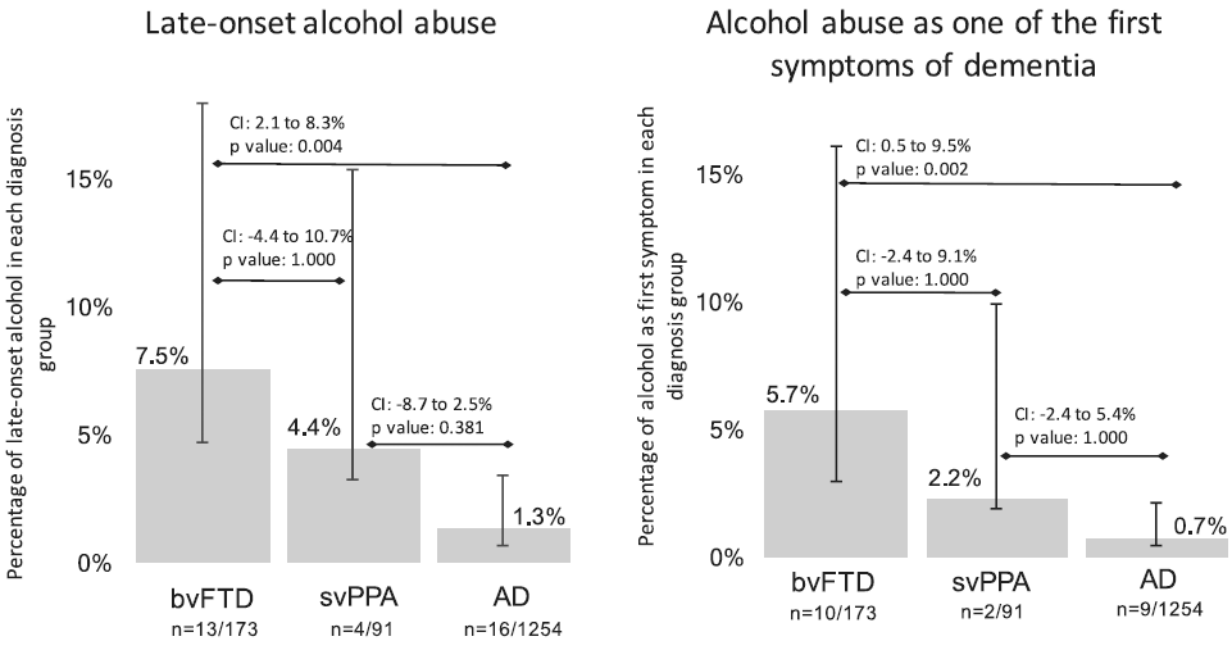

Fig. 1.

Frequency of late-onset alcohol abuse and alcohol abuse as one of the first symptoms of dementia, per diagnosis. The first panel shows the comparisons of the proportions of late-onset alcohol abuse across the cognitive diagnosis: Alzheimer's disease dementia (AD), semantic variant primary progressive aphasia (svPPA), and behavioral variant frontotemporal dementia (bvFTD). The second panel shows the proportions of alcohol as the first symptom (subgroup analyses) across the cognitive diagnosis. The third panel shows the frequency of lifelong alcohol abuse per diagnosis. The Confidence Intervals (CI) refer to the comparisons of the proportions between groups. The error bars depict the 95% CI of the proportions within each cognitive group.

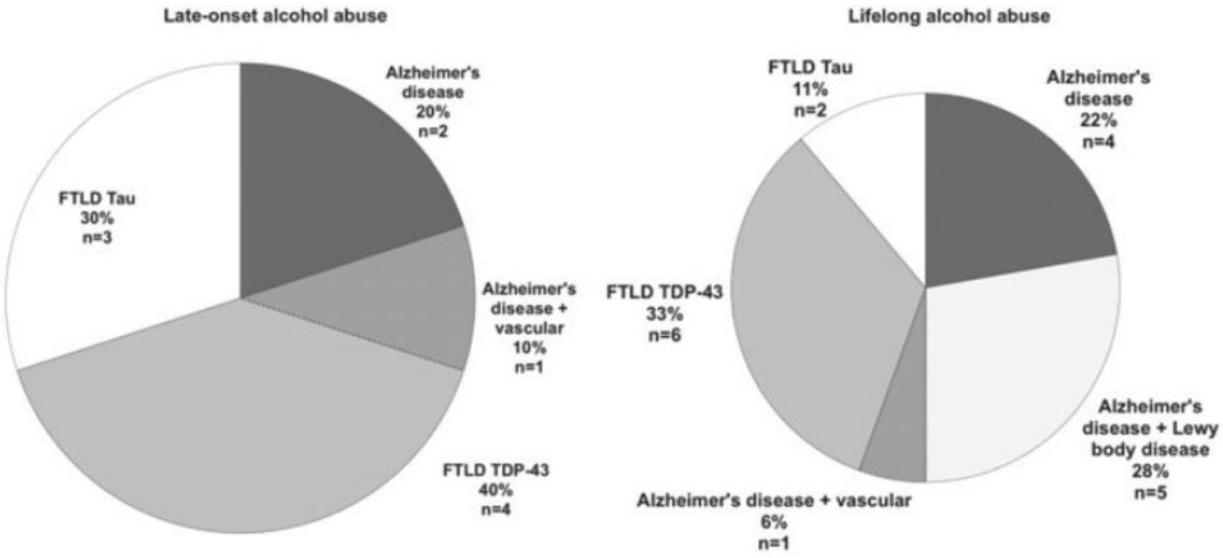

Fig. 2.

Distribution of pathological diagnosis per alcohol status. The proportion of patients with frontotemporal lobar degeneration (FTLD) pathology in the late-onset alcohol abuse was higher than in the lifelong alcohol abuse, where the proportion between FTDL pathology and Alzheimer's disease was similar.

Table 1

Demographic characteristics of the patients per alcohol status

	LO-AA [c] ***n*** **= 33**	**L-AA** ***n*** **= 95**	**No-alcohol abuse** ***n*** **= 1,390**
Age of dementia symptoms onset	60 [54, 68][a]	65 [57, 73]	68 [58, 76][a]
Age of alcohol abuse onset	58 [53, 66]	23 [20, 32]	–
Education (y)	18 [16, 18][a]	16 [14, 18]	16 [13, 18][a]
MMSE at first visit	22 [17, 26]	24 [20, 27]	23 [18, 26]
Female *n*(%)	17 (51)	35 (37)[b]	781 (56)[b]

The values are depicted in medians and [interquartile range].

[a] $p < 0.01$ Late-onset versus No-alcohol.

[b] $p < 0.01$ Lifelong versus No-alcohol.

[c] This group includes the patients in whom alcohol abuse was one of the first symptoms of dementia. MMSE, Mini-Mental State Exam; LO-AA, Late-onset alcohol abuse; L-AA, lifelong alcohol abuse.